NICE National Institute for Health and Care Excellence

For public handouts

Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (CDF review of TA528)

Lead team presentation

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ERG: BMJ TAG

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Company: GSK

3rd August 2021

Key issues

- **Population**
  - How useful is the pooled ITT population for decision-making?
- **Progression free survival**
  - Which assessment of progression free survival should be used?
  - What is the most appropriate extrapolation of progression free survival?
- **Overall survival**
  - How should overall survival for routine surveillance be modelled?
  - What is the most appropriate source of data for the comparator arm?
  - Does the SACT data reduce uncertainties around long-term OS?
- **Time to treatment discontinuation**
  - How should TTD be modelled?
- **Utilities**
  - Are treatment specific utilities appropriate?
- **Dosage**
  - Should prescribed dose data or actual dose receive be used in the model?
- **End of Life**
  - Does non-gBRCAmut 2L+ population meet the end-of-life criteria

Niraparib (Zejula, GSK)

Marketing authorisation November 2017	Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
Mechanism of action	Selective PARP-1 and -PARP-2 inhibitor, which selectively kills tumour cells by preventing repair of damaged DNA
Administration and dose	300 mg once daily (3 x 100 mg capsules) with or without food Commonly used dose used in NOVA trial and supported by clinical practice is 200 mg per day (2 x 100 mg capsules).
List price	List price: £4,500 for 1 pack of 56 x 100 mg capsules, and £6,750 for 1 pack of 84 x 100 mg capsules 28 day cycle cost of 300mg daily: £6,700 28 day cycle cost of 200mg daily: £4,500 Confidential patient access scheme approved (simple discount)

Ovarian cancer: disease background

- Ovarian cancer (OC) occurs in different parts of the ovary or fallopian tubes
- Average age at diagnosis is 65 years
- ~20% of people with high-grade serous ovarian cancer have mutations in breast cancer susceptibility gene (BRCA) 1 or BRCA2 which makes them more likely to respond to treatment with PARP inhibitors
- Main symptoms: persistent bloating, loss of appetite, pelvic or abdominal pain, increased urinary urgency/frequency
- Early stages can be asymptomatic or mimic symptoms of other diseases (leading to late diagnosis)
  - most people have advanced disease at diagnosis (58% have stage III or IV)
- 90% of ovarian cancers arise from epithelial cells; 70% of these are high-grade serous tumours
- 5-year survival in 2013 to 2017 in England was estimated to be 42.9% for all stages, 26.9% for stage III and 13.4% for stage IV disease

Treatment options and maintenance therapy

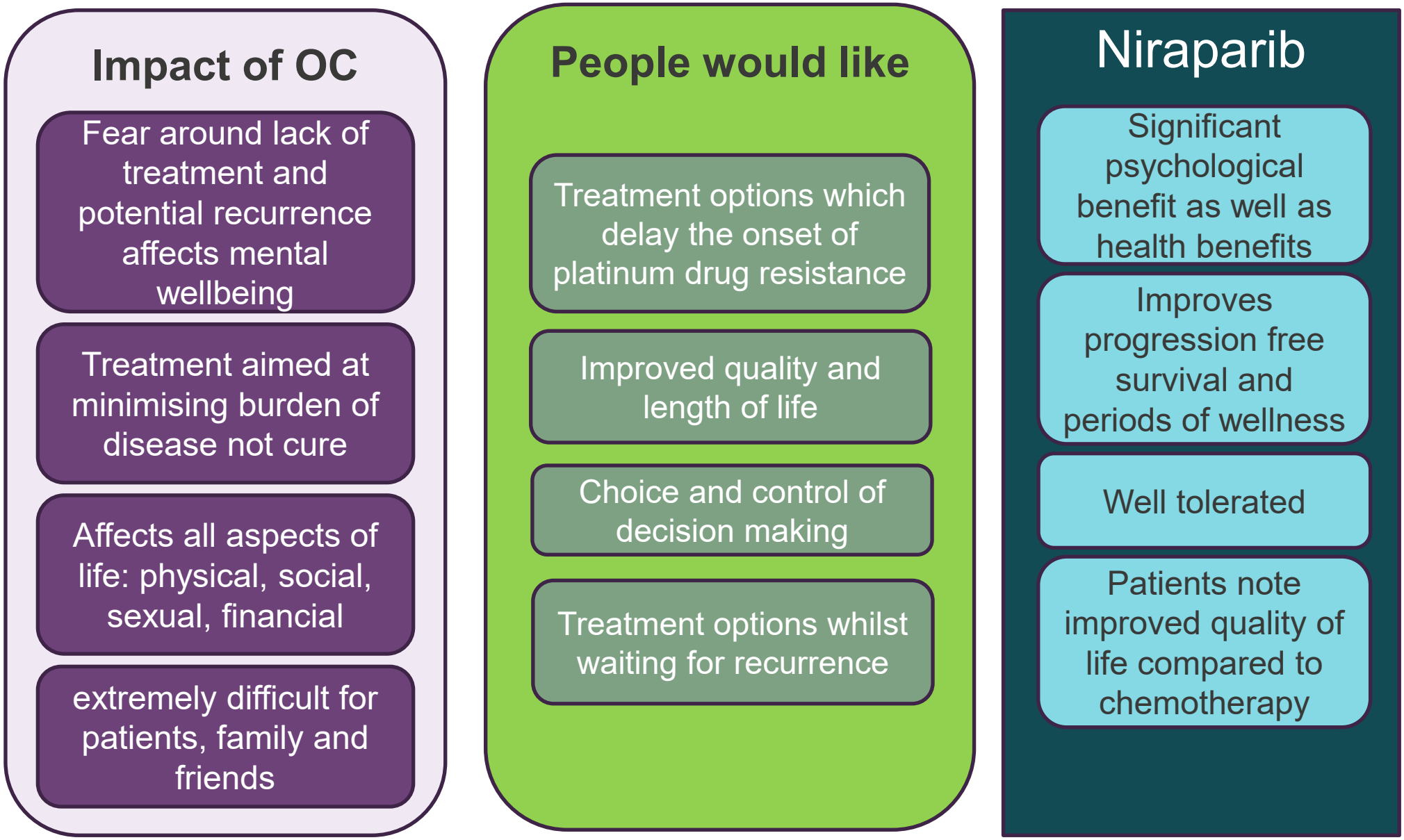
- Platinum-sensitive ovarian cancers progress 6 or more months after platinum-based chemotherapy
- Patients with platinum-sensitive ovarian cancer have a better prognosis and more treatment options
- Maintenance therapy is a treatment taken between different lines of chemotherapy to help maintain progression-free survival (PFS)
- Several PARP inhibitors are available as maintenance therapy after first-line and second-line chemotherapy through the CDF but not through routine commissioning

Diagnostic testing in current practice

Breast cancer susceptibility gene mutation (BRCAmut)	• NHS England commissions genetic testing for (breast cancer genes 1 and 2) BRCA1 and BRCA2 in those that have a pre-test BRCA1 and BRCA2 carrier probability risk of 10% or more • Recommended in NICE clinical guideline (CG)164 • Significant variation across England of the threshold risk and therefore the eligible individuals being offered genetic testing for BRCA1 and BRCA2 • Blood sample generally used for genetic testing. Somatic testing not routine, but becoming more common

Eligible population for niraparib would be tested as 20% of patients with high-grade serous ovarian cancer carry a germline BRCA mutation

Patient organisation perspective



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Patient expert perspective – response to TE

Benefits of niraparib:

- "**Choice** – no current maintenance treatments
- **Best possible care** – prolonging disease free intervals
- **Physical wellbeing** – longer PFS supports recovery from chemo and so enables further treatment cycles
- **Emotional/mental** - delays recurrence so gives time for mental recovery
- **Mode of delivery** – well tolerated given at home"

"Recurrent disease has a **huge impact** on women and their families and the ability to take a treatment that may give them months of PFS where they **can recover physically and emotionally** from chemotherapy treatment and do not have to attend a hospital setting is hugely important"

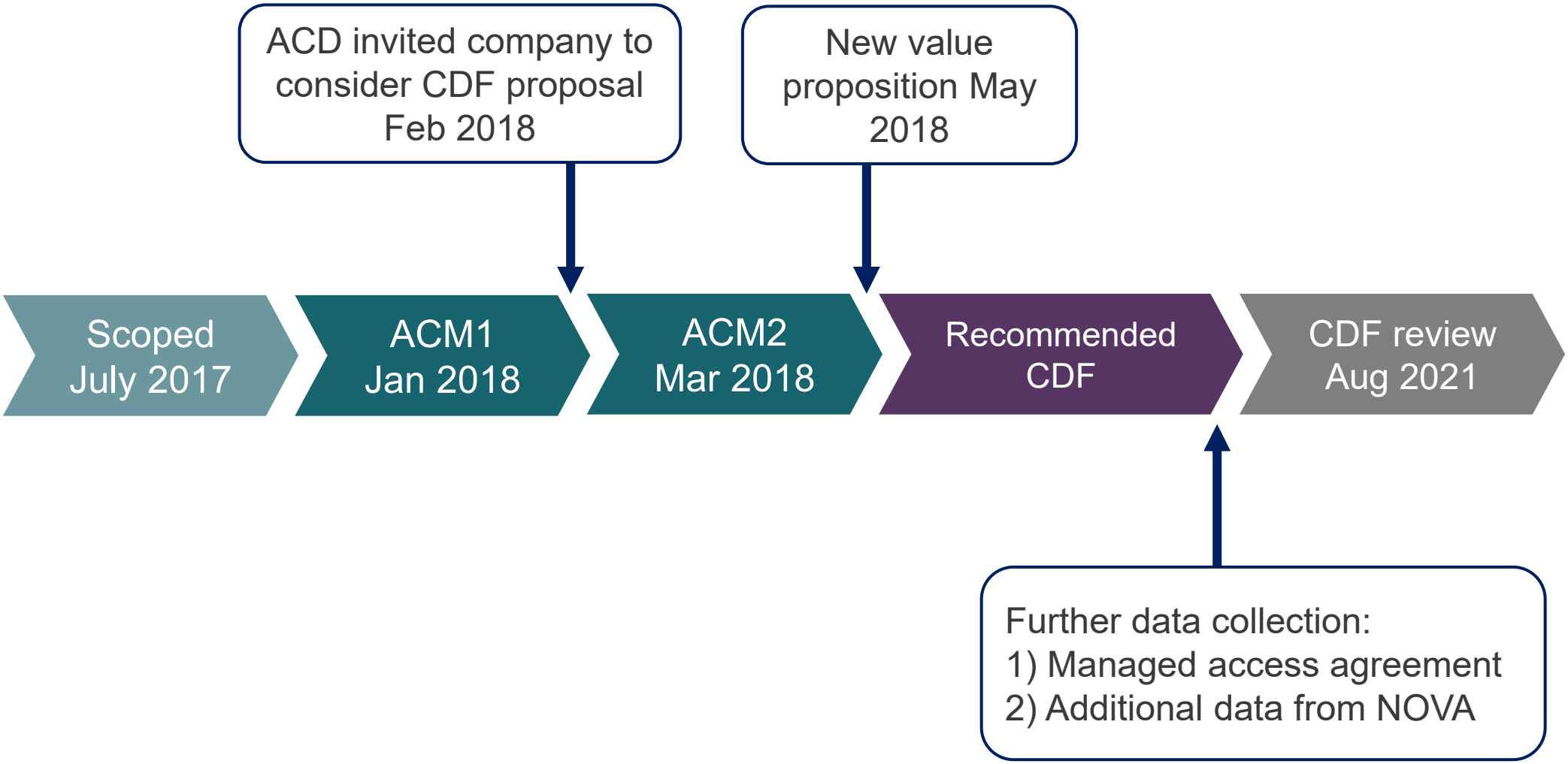
"**Maintenance therapies** like niraparib which **extend the time** between platinum-based chemotherapy may **reduce toxic effects** and **prolong tumour response** to chemotherapy"

"Niraparib is **available to women regardless of BRCA mutation** which means more women will be able to access the treatment"

Clinical expert perspective

- Survival with ovarian cancer is increasing with prevalence now greater than incidence - women are living with ovarian cancer, and living longer
- Niraparib is a well-tolerated drug and the option to start patients at a lower starting dose reduces major toxicity
    - There has been a greater use of the lower dose of niraparib in clinical practice. This lower dose is cheaper and associated with less toxicity
- Key aim of maintenance therapy is to delay progression thereby prolonging survival and the need to restart chemotherapy
- Without maintenance therapy the outlook for women with recurrent ovarian cancer is poor
- Significant prolongation of PFS with niraparib among all groups of patients responding to platinum-based therapy
    - Expected median PFS from placebo arm of PARP inhibitor studies is consistent (median 5.5 months); patients can be expected to be on chemotherapy again around 6 months after the previous course of treatment

Summary of original appraisal TA528

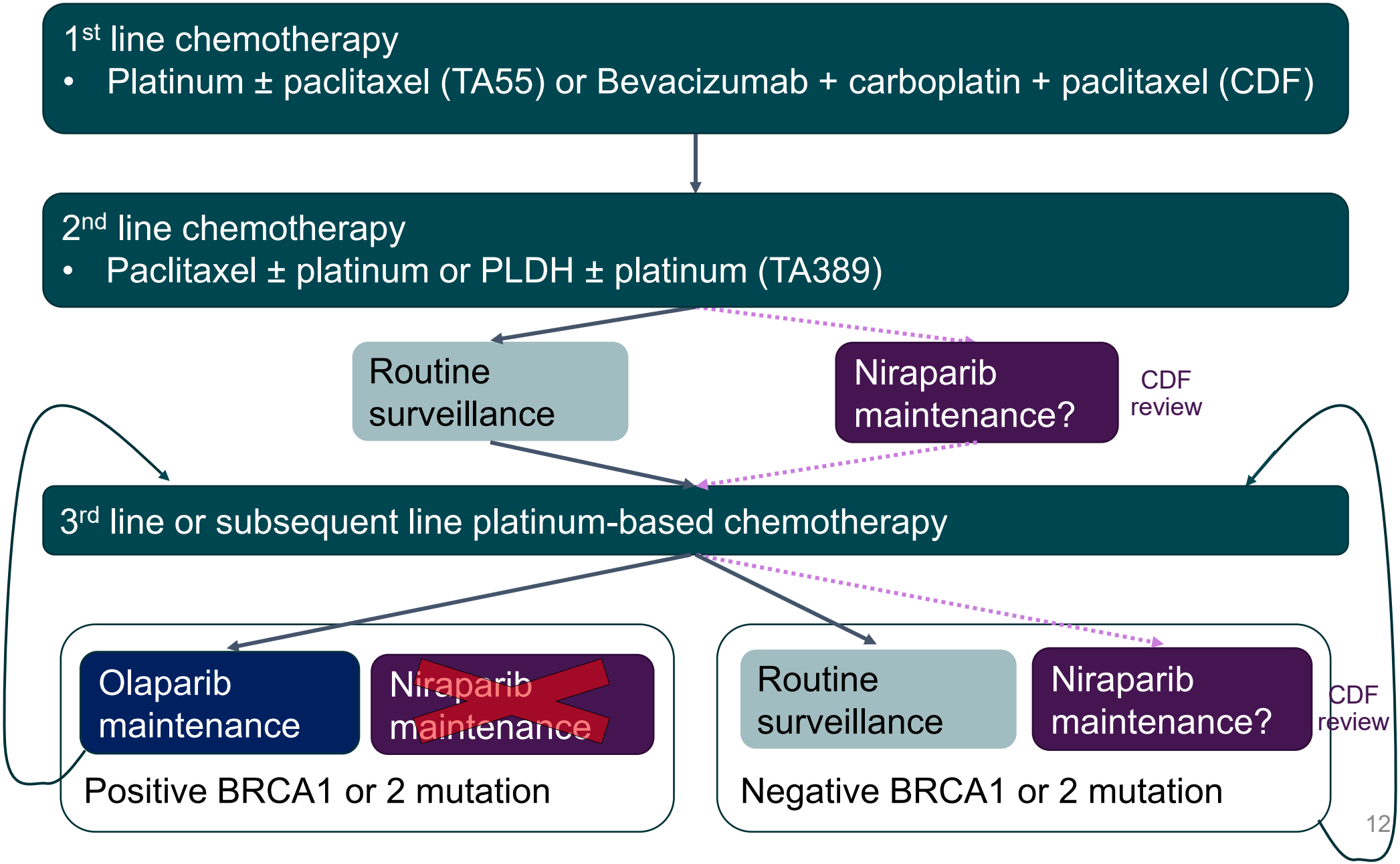


CDF recommendation

- Niraparib is recommended for use within the Cancer Drugs Fund as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults, only if:
  - They have a germline BRCA mutation and have had 2 prior lines of platinum-based chemotherapy (gBRCAmut 2L) or
  - They do not have a germline BRCA mutation and have had 2 or more prior lines of platinum-based chemotherapy (non-gBRCAmut 2L+).

NB. The committee noted that niraparib could not be considered plausibly cost-effective compared with olaparib in people with BRCA mutation who have had 3 or more courses of chemotherapy.

Management of advanced platinum-sensitive ovarian cancer



Key conclusions from TA528

- **Key uncertainties**
  - Extrapolation of progression free survival (PFS)
  - Overall survival (OS) estimates immature at the time
  - Overall survival benefit estimated assuming a ratio for OS and PFS gain
- **Cost effectiveness estimates**
  - Dependent on choice of survival curves to model PFS
  - More conservative ratio for PFS:OS benefit resulted in much higher ICERs for niraparib
- **CDF**
  - Not possible to resolve the uncertainty about the OS benefit with niraparib until mature data from NOVA becomes available
  - Mature PFS and OS data from NOVA (key RCT niraparib vs placebo) and study 19 (olaparib vs placebo) likely to resolve uncertainty around treatment effect and produce more robust cost-effectiveness estimates
  - Plausible potential that niraparib could be cost effective in routine use
- **Data collection**
  - PFS and OS data collection from NOVA and observational data from the systemic anti-cancer therapy (SACT) dataset.
  - Real-world data collected within the Cancer Drugs Fund by Public Health England will support the generalisability of the NOVA data

Key committee conclusions from TA528 (1)

Topic	Committee consideration from TA528 appraisal
Comparators	Niraparib is a maintenance treatment for relapsed platinum-sensitive ovarian cancer. **The relevant comparators are routine surveillance and Olaparib (for people that have had 3 or more courses of platinum-based chemotherapy)**
Clinical evidence	**NOVA was well conducted. Baseline characteristics were well balanced between treatment groups and were representative of people seen in NHS clinical practice in England**
PFS	**Niraparib improves progression-free survival in people with or without a germline BRCA mutation.** Benefit appears to be greatest in people with a germline BRCA mutation
HRD positive tumours	**Homologous recombination deficiency (HRD) testing is not reliable as a means of identifying patients who would/not benefit from treatment**
OS	Immature with multiple factors that could confound the results **No reason that the overall survival benefit will be less than the progression-free survival benefit.** Uncertain if overall survival benefit will be equal to or exceed the progression-free survival benefit More robust estimates of the long-term benefit of niraparib from NOVA in 2020
Effectiveness vs olaparib	**Niraparib has not been shown to be more effective than olaparib**
Adverse events	**The safety profile of niraparib is manageable to patients**

Key committee conclusions from TA528 (2)

Topic	Committee consideration from TA528 appraisal
Model structure	**The model was adequate for decision-making and that the choice of model structure was not critical.**
Extrapolation of PFS	**Choice of survival curves to model progression-free survival had a major impact on the cost-effectiveness results** the best way to model the benefit long-term, beyond the available data from the trial, is very uncertain
Extrapolation of OS	**Ratio of overall survival and progression-free survival gain used as OS data immature. Change in ratio had large impact on cost effectiveness results.** **Not possible to resolve the uncertainty about the overall survival benefit with niraparib until mature data from NOVA become available**
Time to treatment discontinuation	**Time to treatment discontinuation was more reflective of real life clinical practice than IRC assessed progression free survival and therefore the most appropriate to use in the model**
End of Life	Estimated life expectancy with routine surveillance for people without a germline BRCA in the model was 2.87 years **End-of-life criteria for people without a gBRCA mutation are not met**

CDF Review – terms of engagement

Committee's preferred assumptions in TA528 – Terms of engagement

Subject	Committee preferred assumption	Adherent or departing from committee preferred assumptions
Population	The relevant populations are patients with BRCA mutation after 2 courses of platinum-based chemotherapy or without BRCA mutation after 2 or more courses of platinum-based chemotherapy	? company submission uses ITT population which includes a proportion of patients with BRCA mutation who have had 3 or more courses of chemotherapy
HRD+ subgroup	HRD subgroup status is not considered	✓
Progression-free survival	Fully investigate the most appropriate PFS modelling	✓ PFS data unchanged but updated modelling provided
Overall survival	Fully investigate the most appropriate OS modelling using updated clinical trial data	? Niraparib arm uses updated OS data from NOVA. Placebo arm uses Study 19 or Lord et al 2020.
Time-to-treatment discontinuation	NOVA trial data should be used to within the economic model.	✓ Data from the latest available data cut (Oct 2020) for NOVA
End of Life	Niraparib does not meet the end-of-life criteria	✗ Revised. Company propose non-gBRCAmut 2L+ population meets the end-of-life criteria

Primary clinical evidence: NOVA

Design	Phase III, randomised, double-blind, placebo controlled multicentre (10 sites in UK)
Population	• Adults (n=553) with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer • Previously received ≥2 platinum-based regimens • Responsive (partial or complete) to last platinum regimen 2 cohorts: With (n=203) germline BRCA mutation Without (n=350) germline BRCA mutation
Intervention	Niraparib 300 mg (n=372)
Comparator	Placebo (n=181)
Trial outcomes	**Primary:** Progression-free survival (RECIST v1.1 blinded central review) **Secondary:** Time to first and time to second subsequent therapy, chemotherapy-free interval, progression free survival 2, overall survival, quality of life (EQ-5D-5L)
Outcomes to address uncertainties	• OS (used in economic model) • TTD (used in economic model)

Updated clinical evidence: PFS

- TA528 used primary PFS analysis (data cut-off June 2016)
- PFS not assessed after primary analysis; no update to PFS data

Company:
- PFS assessed by an Independent Review Committee (IRC) used in the model
- Assessment of PFS not a key uncertainty in Terms of engagement
- Investigator assessed (IA) PFS was not a defined endpoint in NOVA
- Trial centres not trained, no standardised protocol for assessing progression by investigators
- Included as a sensitivity analysis to ensure robustness of the hazard ratio

ERG:
- Treatment discontinuation determined by investigators (IA TTD).
- IRC PFS is the primary outcome of NOVA but completed retrospectively. Likely to be confounded by informative censoring
- More appropriate to use IA PFS and IA TTD in the model
- Longer median PFS for patients treated with niraparib when assessed by the IRC compared with IA PFS
- Inconsistent assessment (IA data for TTD and IRC data for PFS) leads to a disconnect between PFS and TTD in the economic model (costs and benefits not aligned)
- Impacts on cost effectiveness results

Assessment of progression free survival

	Median PFS (months (95% CI)		Hazard ratio (95% CI)	p-value
	Niraparib (N=138)	Placebo (N=65)		
gBRCAmut				
IRC	21.0 (12.9 to NE)	5.5 (3.9 to 7.4)	0.26 (0.169 to 0.407)	<0.0001
Investigator assessment	14.8 (12.0 to 16.6)	5.5 (4.9 to 7.2)	0.27 (0.182 to 0.401)	<0.0001
non-gBRCAmut	**n=234**	**n=116**		
IRC	9.3 (7.2 to 11.3)	3.9 (3.7 to 5.6)	0.46 (0.339 to 0.615)	<0.0001
Investigator assessment	8.7 (7.3 to 10.0)	4.3 (3.7 to 5.5)	0.53 (0.405 to 0.683)	<0.0001

Abbreviations: BRCA, breast cancer susceptibility gene; CI, confidence interval; gBRCAmut, germline BRCA mutation; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours

- **What is committees view on the assessment of progression free survival?**

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Source: (adapted from CSR Table 25 and Table 28)

Key outcomes NOVA - data cut-off Oct 2020

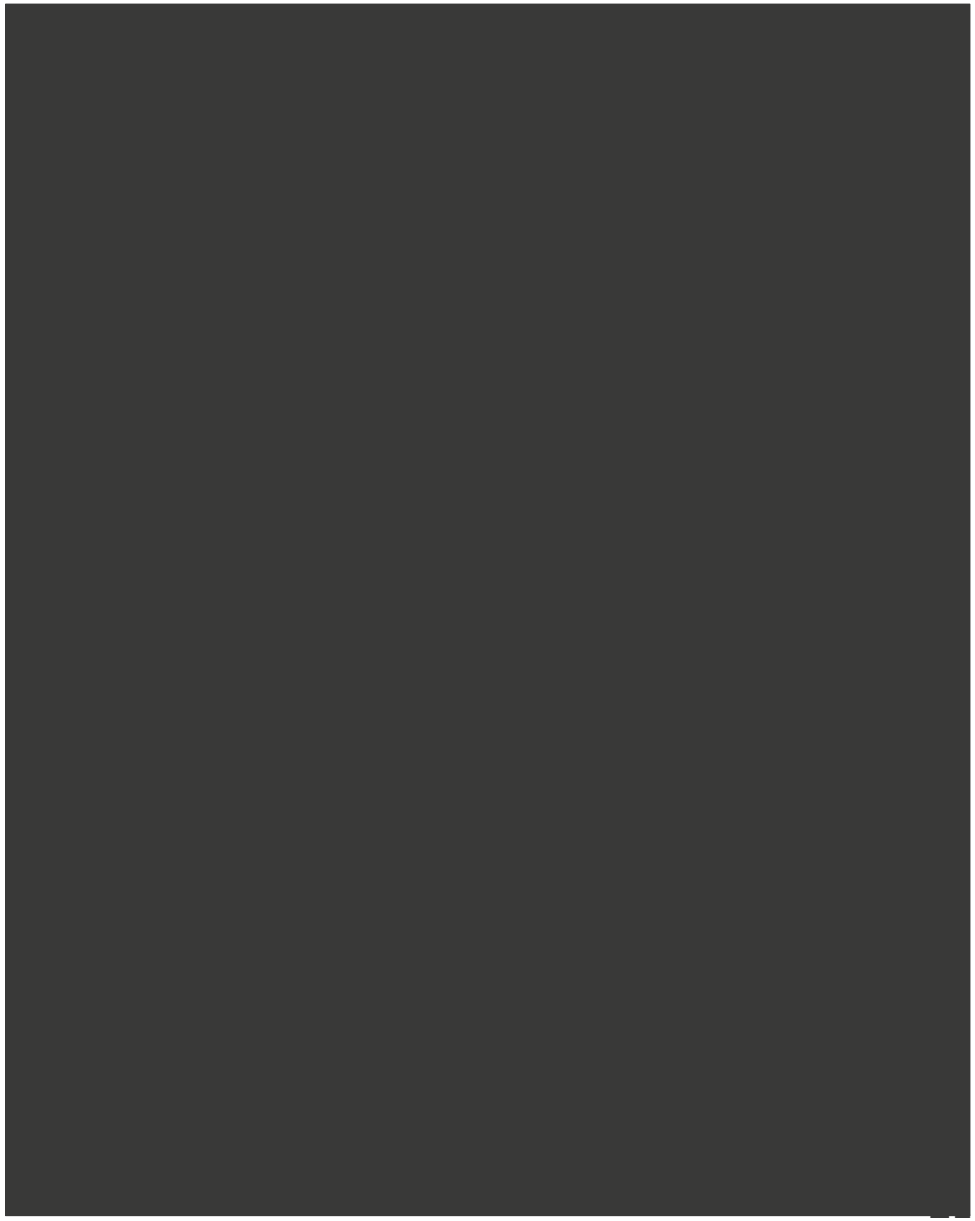
Endpoint	Placebo	Niraparib
Overall survival – gBRCAmut 2L cohort[a]		
Number of patients	30	70
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), p-value	[redacted]	
Overall survival – non-gBRCAmut 2L+ cohort[a,b]		
Number of patients	116	234
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	36.47 ([redacted]	31.11 [redacted]
HR (95% CI), p-value	1.10 (0.83 to 1.46), p =NR	
Time to treatment discontinuation – gBRCAmut 2L cohort[a]		
Number of patients	30	70
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), p-value	[redacted]	
Time to treatment discontinuation – non-gBRCAmut 2L+ cohort[a]		
Number of patients	116	234
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), p-value	[redacted]	

OS Kaplan-Meier curves- data cut-off Oct 2020

gBRCAmut 2L cohort

Source: Figure 1,page 41 of ERG report

non-gBRCAmut 2L+ cohort



Source: Figure 2,page 42 of ERG report

Overall Survival: NOVA data cut-off Oct 2020

- Discontinuation from NOVA ≥80% in both niraparib and placebo arms
- Investigators required to discontinue patients if they were unblinded to the study treatment
- Data entry includes last known survival update or death based on public records
- High missing data in both trial arms (~14%)
- Patients could receive PARP (poly (ADP-ribose) polymerase) inhibitor therapy post-progression

	gBRCAmut 2L (n = 100)		Non-gBRCAmut 2L+ (n = 350)	
Treatment	Niraparib n = 70 (%)	Placebo n = 30 (%)	Niraparib n = 234 (%)	Placebo n = 116 (%)
Number of patients who had subsequent PARPi, n (%)	XXXXX	XXXXX	15 (6.4)	15 (12.9)
Missing information, n (%)	XXXXX	XXXXX	51 (21.8)	31 (26.7)
Number with subsequent PARPi, n (% information was available)	XXXXX	XXXXX	15 (8.2)	15 (17.6)

ERG & Company:

- OS results from NOVA are likely to be confounded and conservative

Company:

Routine surveillance

- Base case: ERG preferred method adopted after TE, uses data from Study 19
- Scenarios: additional data source Lord et al. 2020 and PFS:OS ratio

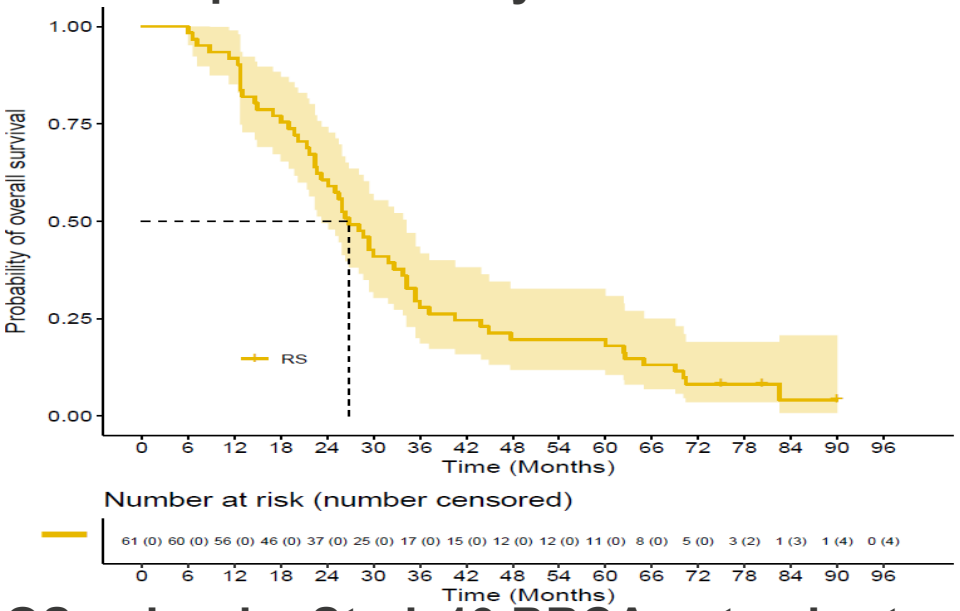
Niraparib arm uses updated OS data from NOVA

Additional evidence for OS - Study 19 (1)

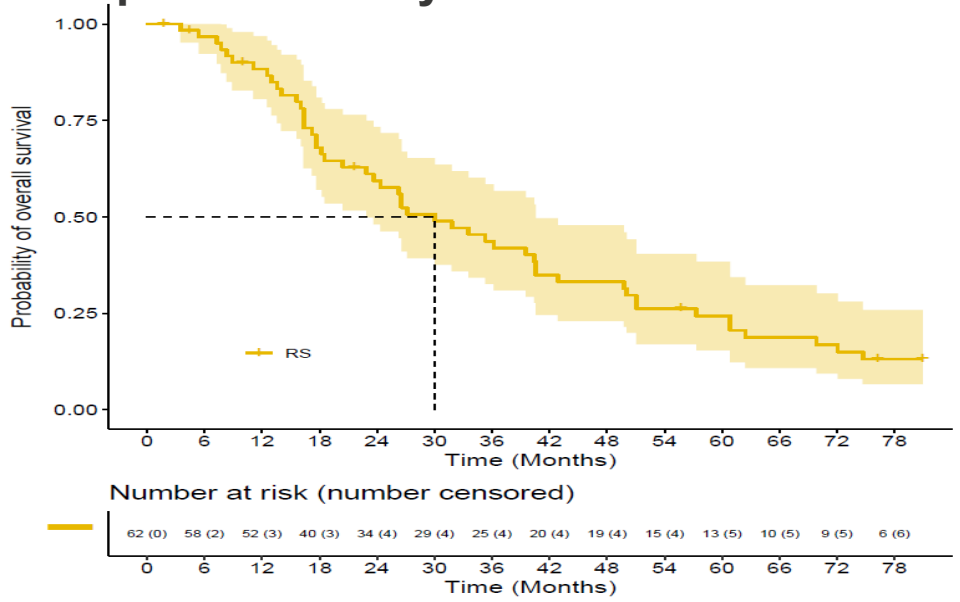
Due to limitations of OS placebo data from NOVA, company base case for routine surveillance is based on long-term extrapolations from the placebo arm of Study 19 or from Lord et al. 2020

	Study 19
Design	Double-blind, placebo-controlled, international multicentre phase II RCT
Population	• Patients with platinum sensitive relapsed ovarian cancer, who are in response to platinum chemotherapy, irrespective of BRCA mutation status
Intervention	Olaparib, 400mg twice daily (N = 136) (BRCAmut n=74, BRCAwt n=62)
Comparator	Placebo (n=129) (BRCAmut n=62, BRCAwt n=61)
Outcomes	• Progression-free survival • Time to first subsequent treatment • Time to second subsequent treatment • Overall survival • Health-related quality of life • Adverse events

OS - placebo Study19 BRCAwt cohort



OS - placebo Study19 BRCAmut cohort



Additional evidence for OS - Study 19 (2)

Characteristic	Study 19 BRCAmut Placebo (n= 62)	NOVA gBRCAmut 2L Niraparib (n=79)	Study 19 BRCAwt Placebo (n= 61)	NOVA Non-BRCAmut 2L+ Niraparib (n=234)
Median age, yr (range)	55 (33–84)	56.6 (37, 83)	63 (49–79)	63 (33–84)
Eastern Cooperative Oncology Group performance status, n (%)				
0	45 (73)	XXXXXX	45 (74)	160 (68.4)
1	15 (24)	XXXXXX	14 (23)	74 (31.6)
Time to progression after penultimate platinum therapy, n (%)				
6 to <12 months	26 (42)	XXXXXX	24 (39)	90 (38.5)
≥12 months	36 (58)	XXXXXX	37 (61)	144 (61.5)
Best response to most recent platinum therapy, n (%)				
Complete	34 (55)		25 (41)	117 (50.0)
Partial	28 (45)		36 (59)	117 (50.0)
Germline BRCA mutation, n (%)				
BRCA1	44 (71)	XXXXXX		
BRCA2	17 (27)	XXXXXX		
BRCA1/2 rearrangement, both	1 (2)	XXXXXX		
Number of patients who received subsequent PARPi				
n/N (%)	14/62 (22.6)	XXXXXX	3/61 (4.9)	XXXXXX

ERG:

- Differences in performance status, response to platinum-based therapy, prior bevacizumab use and subsequent PARP inhibitor use
- Small differences important as naïve comparison of niraparib-NOVA and placebo-Study 19
- Naïve comparison may overestimate the difference between niraparib and placebo

NOVA: pooled intention-to-treat population

Company:

- Pooled intention-to-treat (ITT) analyses formed by combining the two randomised patient cohorts of the NOVA trial
- Provides an additional comparison allowing OS outcomes to be compared with UK-based real world evidence (RWE) - Lord et al. 2020
- Aligned with the marketing authorisation for niraparib
- Reflects the current use in UK clinical practice

Population (pooled ITT)	PFS		
	Progression or death		HR (95% CI)
	Placebo	Niraparib	
June 2016	[redacted]	[redacted]	[redacted]

Population (pooled ITT)	OS		
	Time to death		HR (95% CI)
	Niraparib	Placebo	
October 2020	[redacted]	[redacted]	[redacted]

ERG:

- Outside the scope of the CDF review, full population not included in terms of engagement
- ITT population *post-hoc*
- Not restricted to gBRCAmut patients who have only had two lines of platinum-based chemotherapy. Efficacy of niraparib versus routine surveillance likely to be overestimated as a proportion of gBRCAmut have had 3 or more courses of chemotherapy

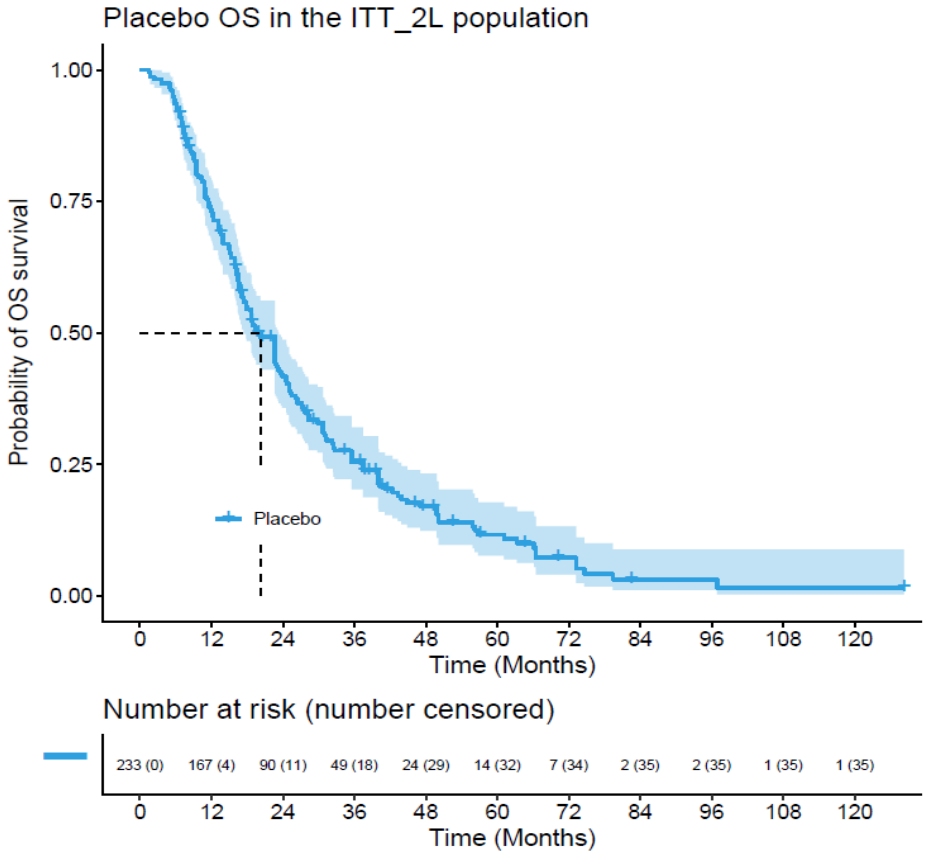
- **What is committees view on the pooled ITT population?**

Additional evidence for OS-Lord et al. 2020

A 2020 study investigating survival outcomes from standard of care (routine surveillance) across 13 National Health Service Trusts in the UK

	Lord et al. 2020
Design	Observational, retrospective chart review
Population	Patients who had completed two lines of platinum-based chemotherapy with evidence of an objective response
Intervention	Routine surveillence BRCA status unknown for 81%
Comparator	N/A
Outcomes	1°: Overall survival 2°: progression free survival 2°: overall survival by subsequent line of treatment

Overall survival in patients treated with routine surveillance;



Source of comparator	Study 19 - placebo		NOVA - placebo		Lord et al. 2020 – routine surveillance
	BRCAwt	BRCAmut	Non- BRCAmut	BRCAmut	
Overall survival	26.6 months	30.2 months	36.5 months	XXX months	19.8 months
% died	93.4%	80.6%	XXX%	XXX%	NR

Systemic Anti-Cancer Therapy (SACT) data

June 2019 data cut off

	gBRCAmut 2L (N=XXX)	Non-gBRCAmut 2L+ (N=XXX)
Overall survival		
Median follow up	XXXXXXX	XXXXXXX
Median OS	XXXXXXX	XXXXXXX
Time to treatment discontinuation (TTD)		
Median follow up	XXXXXXX	XXXXXXX
Median TTD	XXXXXXX	XXXXXXX

- SACT cohort slightly older and more frail than NOVA cohort
- OS data not used in company base case model due to limited availability of baseline characteristics limiting comparison with NOVA
  - SACT OS used in model as company scenario analysis
- PFS outcomes not collected in SACT so company simulated from NOVA TTD using a PFS:TTD ratio of XXX for gBRCAmut and XXX for non-gBRCAmut
- OS, TTD and PFS XXXXXX in SACT than observed in NOVA
- TTD used in model as company scenario analysis
- Routine surveillance arm simulated using NOVA PFS HR applied to niraparib SACT curve, and a 1:1 PFS:OS ratio

Key issues

- **Population**
  - How useful is the pooled ITT population for decision-making?
- **Progression free survival**
  - Which assessment of progression free survival should be used?
  - What is the most appropriate extrapolation of progression free survival?
- **Overall survival**
  - How should overall survival for routine surveillance be modelled?
  - What is the most appropriate source of data for the comparator arm?
  - Does the SACT data reduce uncertainties around long-term OS?
- **Time to treatment discontinuation**
  - How should TTD be modelled?
- **Utilities**
  - Are treatment specific utilities appropriate?
- **Dosage**
  - Should prescribed dose data or actual dose receive be used in the model?
- **End of Life**
  - Does non-gBRCAmut 2L+ population meet the end-of-life criteria

Cost-effectiveness evidence

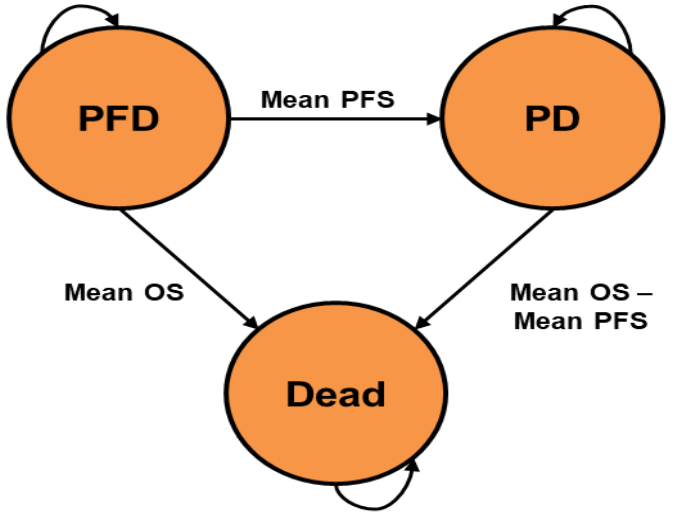
Economic model

TA528 FAD conclusion:

- Committee accepted that model was adequate for decision-making and choice of model structure was not critical to decision-making
- Company explored other model structures, including a partitioned survival model (PSM), and stated that cost-effectiveness results differed by no more than £1,000 per QALY gained

Company:

- No model changes as specified in Terms of Engagement
- 3 health states: progression free disease (PFD), progressive disease (PD), and dead
- 40 year time horizon, cycle length is 28 days
- Based on mean values for parameters
- Estimates survival curves for PFS and OS to calculate the area under the curve (AUC) and calculate the mean time spent in the health state



ERG:

- Movements through health states determined by mean time spent in the health state
- Means based model (MBM) justified because of immature OS data in TA528 - more mature OS data from NOVA makes means-based model inappropriate
- Company's PSM not presented to the ERG or committee for validation. Post TE, company submitted CE results from original PSM
- PSM model seems to have used constructed OS curve that had a mean survival equal to the estimate from their means-based model rather than extrapolating OS data from the trial
- PSM using extrapolated OS data most suitable method now mature OS data available

Estimating PFS beyond the trial (1)

[redacted]

[redacted]

Proportion of patients progression-free

Year	Lognormal	Hazards k=1 spline	Weibull
5	21.75%	21.36%	7.35%
10	8.97%	5.78%	0.18%
15	4.74%	1.69%	0.00%
20	2.85%	0.52%	0.00%

Original company base case

Base case & ERG preferred

TA528 ERG preferred

Year	Normal k=1 spline	Hazards k=1 spline	Lognormal
5	9.22%	9.09%	2.91%
10	3.89%	3.10%	0.50%
15	1.92%	1.33%	0.15%
20	0.75%	0.65%	0.06%

Company base case

ERG preferred

TA528 ERG preferred

Estimating PFS beyond the trial (2)

PFS for the gBRCAmut 2L subgroup

Company:

- ERG's hazard k=1 (ERG preferred) a conservative estimate, but accepted for updated base-case analysis
- Lognormal curve is clinically plausible, used in scenario analysis
- Reduced rate of disease progression compared to the hazard k=1 curve
- Patients who remain progression-free after 10 years will have a reduced risk of progression

PFS for the non-g*BRCA*mut 2L+ subgroup

Company:

- Normal k=1 spline is clinically plausible, hazards k=1 spline estimates almost identical
- Statistical fit for normal k=1 spline better than hazards k=1 spline (AIC [redacted] vs [redacted])
- Study 19 reports that ~14% of olaparib patients were on treatment and therefore progression-free after 5 years
- PFS estimates lower than normal k=1 spline do not fully capture long term impact of niraparib

ERG:

- Company aligns with ERG preferred PFS extrapolation for the **gBRCAmut 2L** subgroup
- **non-gBRCAmut 2L+** hazards k=1 spline conservative but chosen on statistical and visual fit
- Hazards k=1 spline long-term (15 years onwards) estimates aligned with PFS estimates for the gBRCAmut 2L subgroup
- Hazards k=1 spline more clinically valid for non-gBRCAmut 2L+ subgroup

OS extrapolation: source of data

TA528:

- Immature OS data. Committee preferred to assume that all patients, regardless of treatment, have the same post-progression risk of death (ratio of overall survival to progression-free survival of 1:1)

Company

- OS results from NOVA likely to be confounded (missing data and cross over)
- 1:1 used ratio to estimate OS for routine surveillance arm in original base case, after TE presented as a scenario analysis

ERG

- Disagrees with use of a PFS:OS ratio because of lack of consistent evidence around relationship between PFS and OS in advanced or metastatic cancer
- Prefers to use OS data from Study 19 for routine surveillance arm (as in TA528) – naïve comparison with no adjustments for differences between subgroups

Technical engagement response:

- Company accepts ERG approach for updated base case
- PFS:OS 1:1 ratio presented as scenario analysis

- **What's committee's view on how best to model overall survival for routine surveillance?**

OS extrapolation – naïve comparison

OS Kaplan Meier and lognormal distribution for niraparib (NOVA) and routine surveillance OS from Study 19

ERG

- OS data from 2020 data cut used for niraparib arm
- Withdrawal or crossover to PARP inhibitors in the placebo arm substantial, OS estimates confounded
- Lognormal curve appropriate for the extrapolation of OS for both niraparib and routine surveillance

Subgroup	gBRCAmut 2L	non-gBRCAmut 2L+
Mean incremental niraparib PFS	2.96 years	1.09 years
Mean OS (niraparib)	XXXXXXX	XXXXXXX
Mean OS (Study 19 routine surveillance)	3.70 years	2.97 years

Time to treatment discontinuation

[redacted]

[redacted]

Company:

- Lognormal distribution for the gBRCAmut 2L subgroup
- Log-logistic distribution for the non-gBRCAmut 2L+ subgroup based on best statistical fit.
- Base case updated after clarification to include a cap on TTD so it could not exceed PFS

ERG:

- TTD cap for the non-gBRCAmut 2L+ subgroup applied incorrectly
- Gompertz distribution captures the tail of the KM curve for non-gBRCAmut 2L subgroup
- Longer TTD estimates, while fitting the observed data better

	gBRCAmut 2L	non-gBRCAmut 2L+		
		Company	ERG	SACT
% on treatment at 10 yrs	[redacted]	[redacted]	[redacted]	[redacted]
Mean time niraparib maintenance treatment	[redacted] years	[redacted]	[redacted]	[redacted]

NICE

Utility values

TA528: treatment-specific utility values based on EQ-5D-3L data mapped from NOVA

Company:

- Use later 2020 data-cut from NOVA
- Mixed effect linear regression model niraparib associated with improved quality of life compared to routine surveillance (p-value < 0.05)

Health state	value
Niraparib progression-free disease	XXXX
Niraparib progressed disease	XXXX
Placebo progression-free disease	XXXX
Placebo progressed disease	XXXX

ERG

- Utility values based on progression status preferred
- Adverse event rate higher for niraparib unlikely to be associated with higher health-related quality of life

Health state	Utility value
Progression-free disease	XXXXX
Progressed disease	XXXXX

Technical engagement response

- Company highlights that treatment-specific values were taken from NOVA and capture lowering of symptoms associated with disease and previous treatments
- Also highlights positive impact on mental health for patients to be receiving active treatment rather than watch and wait approach not captured in the model

- **What is committees view on the utilities used in the model?**
- **What is committees view of niraparib vs routine surveillance compared to niraparib vs placebo?**

Dosing of niraparib

Company:

- Amended mean cost for niraparib based on updated dose data from 2020 NOVA data-cut
- Updated dose data based on actual dose consumed (dispensed dose minus returned dose per cycle)
- NOVA 2020 dosing data captured the dose returned by patients to the investigator during the trial
- TA528, dose reflected prescribed dose as weighted average

ERG:

- Niraparib doses prescribed unlikely to be returned and reused in NHS
- Committee preference in TA528 was to use prescribed dose
- Prefers to use prescribed dose

Technical engagement response

- Company states that dosing in clinical practice would be lower than prescribed dose in trial because patients may have dose down-titrated to manage adverse effects. They could then reuse their own prescribed capsules in future and new prescriptions could be delayed, leading to overall reduced prescriptions.

- **What is committees view on how niraparib dosing should be costed in the model?**

SACT data: overall survival

[redacted]

Non-gBRCAmut
Company used log-logistic
ERG prefer Weibull as clinical expert considered survival beyond 7 years unlikely
Company accepts ERG curves although notes conservative

Overall survival - gBRCAmut
Company use log-logistic
ERG prefer generalised gamma as more conservative
Company accepts ERG curves although notes conservative

[redacted]

Does the SACT data reduce uncertainties around long-term OS?

RWE: Niraparib SACT ITT outcomes vs to Lord et al. 2020

Company:

- Scenario analyses used long-term extrapolations of OS data from Lord et al. (2020) to model routine surveillance OS
- Lognormal curve was considered the most plausible curve based on statistical and visual fit
- Presents data on niraparib compared to published, UK-based, RWE OS outcomes of patients on routine surveillance
- Lord et al. 2020 publication is not split into BRCA subgroups, and therefore can only be compared versus ITT population
- Scenario using niraparib SACT ITT outcomes to Lord et al. 2020 outcomes compares UK RWE vs UK RWE data

ERG:

- ITT population in NOVA includes gBRCAmut patients who had 3+lines of chemotherapy.
- Median number of lines of chemotherapy for Lord et al. was 3 (22% received more than 4). SACT gBRCA cohort was limited to 2 lines of prior chemotherapy.

Cost-effectiveness results

Base case assumptions

Key issue(s)		Company's base case before technical engagement	Change(s) made in response to technical engagement	ERG preferred assumptions
PFS	gBRCAmut 2L	Lognormal curve	Hazard k=1 spline	Hazard k=1 spline
	Non-gBRCAmut 2L+	Normal k=1 spline	N/A	Hazard k=1 spline
Overall survival for routine surveillance		1:1 PFS:OS ratio	Study 19 for routine surveillance (lognormal)	Study 19 for routine surveillance (lognormal)
Time to treatment discontinuation		Log-logistic for non-gBRCAmut 2L+	N/A	Gompertz for non-gBRCAmut 2L+
Utilities		Treatment-specific utility values based on EQ-5D-3L data mapped from NOVA	N/A	Health state specific utility values based on progression status and removal of disutility associated with adverse events
Dosage		Actual dose consumed (dispensed dose minus returned dose per cycle) from updated NOVA	N/A	Prescribed dose data from TA528
SACT scenario analyses		OS curves for both subgroups loglogistic	Generalised gamma for gBRCAmut 2L and Weibull for non-gBRCAmut 2L+	Generalised gamma for gBRCAmut 2L and Weibull for non-gBRCAmut 2L+

Company base case results (deterministic)

g*BRCA*mut 2L population

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,185

Non-g*BRCA* 2L+ population

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,608

ERG base case results (deterministic)

g*BRCA*mut 2L population

Technologies	Incremental		ICER (£)	
	Costs (£)	QALYs		Cumulative
Company base case	XXXXXX	XXXXXX	22,185	-
Progression based utilities	XXXXXX	XXXXXX	23,685	23,685
Prescribed dose	XXXXXX	XXXXXX	25,663	27,399
ERG base case	XXXXXX	XXXXXX	**27,399**	**-**

Non-g*BRCA* 2L+ population

Technologies	Incremental		ICER (£)	
	Costs (£)	QALYs		Cumulative
Company base case	XXXXXX	XXXXXX	39,608	-
PFS Hazard k=1 spline	XXXXXX	XXXXXX	39,634	39,990
TDD using Gompertz	XXXXXX	XXXXXX	44,032	42,493
Progression based utilities	XXXXXX	XXXXXX	44,712	48,096
Prescribed dose	XXXXXX	XXXXXX	42,601	51,684
ERG base case	XXXXXX	XXXXXX	**51,684**	**-**

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SACT data: scenario analysis results

SACT gBRCAmut 2L subgroup	Results per patient	Niraparib	Routine surveillance	Incremental value
Company original SACT analysis	Total costs (£)	XXXXXX	XXXXXX	XXXXXX
	QALYs	XXXXXX	XXXXXX	XXXXXX
	ICER (£/QALY)			17,930
Updated after TE Generalised gamma distribution for OS	Total costs (£)	XXXXXX	XXXXXX	XXXXXX
	QALYs	XXXXXX	XXXXXX	XXXXXX
	ICER (£/QALY)			18,312
ERG's results (Generalised gamma distribution for OS)	Total costs (£)	XXXXXX	XXXXXX	XXXXXX
	QALYs	XXXXXX	XXXXXX	XXXXXX
	ICER (£/QALY)			21,683
SACT non-gBRCAmut 2L+				
Company original SACT analysis	Total costs (£)	XXXXXX	XXXXXX	XXXXXX
	QALYs	XXXXXX	XXXXXX	XXXXXX
	ICER (£/QALY)			35,346
Updated after TE Weibull distribution for OS	Total costs (£)	XXXXXX	XXXXXX	XXXXXX
	QALYs	XXXXXX	XXXXXX	XXXXXX
	ICER (£/QALY)			37,986
ERG's results Weibull distribution for OS	Total costs (£)	XXXXXX	XXXXXX	XXXXXX
	QALYs	XXXXXX	XXXXXX	XXXXXX
	ICER (£/QALY)			45,265

Company scenario analyses - pooled ITT

Basecase		Scenario	ICER (£/QALY)
			35,579
Overall Survival	Extrapolated trial data from Study 19 for RS OS	Extrapolated trial data from Lord et al. 2020 for RS OS	**23,147**
		1:1 PFS:OS ratio for RS OS	**25,875**
Time to treatment discontinuation	Niraparib data sourced from NOVA 2020	Niraparib TTD data sourced from SACT	**21,782**
• **RS OS extrapolated trial data from Study 19** • **Niraparib TTD data sourced from NOVA 2020**		• Extrapolated trial data from Lord et al. 2020 for RS OS • Niraparib TTD data from SACT	**14,238**
• **RS OS extrapolated trial data from Study 19** • **Niraparib TTD data sourced from NOVA 2020**		• 1:1 PFS:OS ratio for RS OS • Niraparib TTD data from SACT	**15,893**

Company scenario analyses

gBRCAmut 2L

	Basecase	Scenario	ICER
0			22,185
1	Extrapolated trial data from Study 19 for RS OS	PFS:OS ratio of 1:1	21,838
2	Niraparib TTD using loglogistic	Data from SACT - non-gBRCAmut 2L	20,769
3	-	Scenario 1 and 2	20,445
4	Progression-free survival extrapolated with hazard k=1 spline	Lognormal curve for PFS	22,205
5		Normal k=1 flexible curve for PFS	21,900
6	Treatment specific utilities	Progression based utilities	23,685
7	Actual niraparib dose NOVA 2020	Planned niraparib dose NOVA 2016	25,663

non-gBRCAmut 2L+

	Basecase	Scenario	ICER
0			39,608
1	Overall survival for RS	PFS:OS ratio of 1:1	36,449
2	Niraparib TTD using loglogistic	Data from SACT - non-gBRCAmut 2L	26,299
3	-	Scenario 1 and 2	24,204
4	Treatment specific utilities	Progression based utilities	44,716
5	Actual niraparib dose NOVA 2020	Planned niraparib dose NOVA 2016	42,601

End of life considerations
Non-gBRCAmut 2L+ population

- Not considered to meet end of life criteria in TA528 because estimated life expectancy with routine surveillance in the model was 2.87 years

Criterion	Data source	Overall survival	
		Median	Mean
Short life expectancy, normally < 24 months	SACT non-gBRCAmut 2L+ niraparib arm (company states routine surveillance arm likely lower)	22.6 months	
	Lord et al. 2020 ITT routine surveillance arm median OS (company states non-gBRCA only population will have lower OS)	19.3 months	
	Company base case model – routine surveillance		XXXXxxxXX
	Company model using SACT data with 1:1 PFS:OS ratio using Weibull curve-routine surveillance		XXxxxxXXXX

End of life considerations
Non-gBRCAmut 2L+ population

Criterion	Data source	Mean increase in OS
Extension to life, normally of a mean value of ≥ 3 months	Company base case model	[redacted]
	Scenario analysis PFS:OS 1:1 ratio	[redacted]
	SACT niraparib OS data and using the PFS:OS 1:1	[redacted]
	SACT ITT niraparib OS data and Lord et al routine surveillance	[redacted]

Equalities

- No equalities issues identified